May 24, 2023

Dear Friends,

Thank you for your ongoing support and trust in me. It means a lot. Your encouragement has been vital in our work. In terms of our therapeutic development for Wolfram syndrome, we're making good progress. Let me share the latest updates with you.

Ongoing clinical trial

The urgent need for new treatments for Wolfram syndrome, encompassing both oral and injectable drugs, cannot be overstated. In partnership with Amylyx Pharmaceuticals, we're advancing the development of AMX0035, an oral drug aimed at targeting the upstream disease mechanisms of Wolfram syndrome. For further insight into AMX0035's effect on endoplasmic reticulum stress and mitochondrial dysfunction, we invite you to read our recent article on this topic here: https://insight.jci.org/articles/view/156549.

In 2020, the US FDA acknowledged the potential of AMX0035 by granting it orphan drug status for the treatment of Wolfram syndrome. Leveraging data from the longitudinal study and the dantrolene trial, we have designed a protocol to ensure patient safety while accurately assessing the effectiveness of AMX0035. We're gratified to announce that this protocol has earned approval from both the US FDA and the Institutional Review Board at Washington University Medical Center. As a result, we've initiated a clinical trial of AMX0035 in adult patients with Wolfram syndrome: https://beta.clinicaltrials.gov/study/NCT05676034. Our trial is progressing favorably, and I am committed to sharing updates on our progress whenever possible. Please understand that certain regulatory constraints may limit the frequency and extent of these updates.

The 8th International Wolfram Syndrome Symposium in the UK

The 8th International Wolfram Syndrome Symposium in London, a notable event for specialists in this rare genetic disorder, promoted fresh collaborations and the latest research insights in April this year: https://wolframsyndrome.wustl.edu/highlights-from-the-8th-international-wolfram-syndrome-symposium-hope-on-the-horizon/. Acknowledgments go to Stephanie Snow Gebel, Saad Naseer, MD, Tracy Lynch, Gina Isherwood, PhD, and Nolwen LE FLOCH for their organizational efforts and support.

Main focuses included establishing clinical guidelines, investigating novel biomarkers (such as ER stress, mitochondrial dysfunction, dysregulated calcium homeostasis, brainstem atrophy), advancing gene therapy, listing international trial sites, linking patient registries, and designing innovative trial protocols. These initiatives aim to improve diagnosis, treatment, early detection, disease monitoring, and trial design.

The symposium sparked hope and commitment to confront Wolfram Syndrome. With ongoing collaboration, the future offers potential for significant advancements in comprehending and treating this intricate disorder.

Gene Editing Therapy

Wolfram syndrome arises due to pathogenic alterations in the WFS1 gene. An effective strategy for managing this condition involves rectifying these gene alterations. Our team has partnered with Dr. Catherine Verfaillie, Dr. Lies De Groef , and Dr. Lieve Moons at Katholieke Universiteit Leuven, Belgium, to apply an advanced gene-editing technique known as Base Editing. We have conducted a successful preclinical trial utilizing induced pluripotent stem cells (iPSCs) obtained from Wolfram syndrome patients, and intend to assess this technique in our humanized mouse model of Wolfram syndrome. We have also been investigating the use of Prime Editing to rectify pathogenic alterations in the WFS1 gene associated with Wolfram syndrome. This technique is regarded as the most advanced gene-editing method presently available, and our collaboration with Dr. David Liu's team at Harvard/MIT is pivotal to this endeavor. Our ultimate objective is to employ this therapeutic approach in treating our patients.

Regenerative Therapy for Optic Nerve Atrophy – Gene Therapy and Mesenchymal Stem Cell Transplantation

We are actively researching regenerative therapy as a potential solution to halt and possibly reverse the progression of optic nerve atrophy. We have devised two strategies for achieving this aim.

The first strategy encompasses the delivery of a regenerative factor, known as MANF, into the eyes of patients diagnosed with Wolfram syndrome. We employ a viral vector for this purpose. MANF is a distinctive factor that not only provides protection against ER stress but also stimulates the proliferation of ER-stressed cells.

The second strategy involves administering mesenchymal stem cells into the patients' eyes. These cells, which can be sourced from adipose tissue and bone marrow, have shown promise. Research indicates that the transplantation of mesenchymal stem cells fosters retinal ganglion cell survival and promotes regeneration in rodent models suffering from optic nerve damage.

We are presently conducting preclinical studies to evaluate both the MANF and mesenchymal stem cell methodologies in cell and rodent models of Wolfram syndrome. This is to determine their effectiveness in treating optic nerve atrophy. Our ultimate goal is to initiate a clinical trial for regenerative therapy targeting optic nerve atrophy within the forthcoming 3-7 years.

Clinical service

At the Washington University Medical Center’s Center for Advanced Medicine, we have established the Wolfram Syndrome Clinic program, aimed at improving clinical care for patients with Wolfram syndrome and related disorders, including WFS1-related deafness and optic nerve atrophy.

Our program provides genetic evaluations, education, and counseling services to patients and family members of all ages who have either been diagnosed with Wolfram syndrome, are suspected of having it, or have WFS1-related disorders.

Our team collaborates with other specialists, including neurologists, neuro-ophthalmologists, urologists, medical geneticists, and endocrinologists at our medical center, to provide personalized management plans. We strive to see patients either on the same day or within two consecutive days. Our services are available to both pediatric and adult patients.

Patients in the US
If you're in the US, please call Christine Manning, RN, Nurse Coordinator, at 314-747-7055 or 314-362-3500. Let her know that you or your family member has Wolfram syndrome or WFS1-related medical conditions and need to make an appointment. Once we review your medical records, Dr. Urano or his staff will contact you to discuss which specialists you may need to see.

Sending Medical Records via Fax
Please fax your medical records to 314-747-7065.

Referrals via Fax for both Missouri patients and out-of-state patients
Please fax your referral request to 314-747-7065.

International Patients
International patients are welcome to contact our international patient care office to schedule an appointment by calling +1-314-273-3780 or sending an email to Internationalpatients@wustl.edu.

Conclusion
That wraps it up for today! Our work on therapeutic development for Wolfram syndrome really shows how hard our team's been working and the never-give-up spirit of the people and families dealing with this condition. We've seen some really encouraging results which keep us optimistic for what's next. We know there's still a bunch of challenges to tackle, but we're not backing down. We're all in, pushing for breakthroughs that could make a big difference for those living with Wolfram syndrome. I will keep on updating you about our progress. Thank you again for your continued support.

Sincerely yours,
Fumi

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https://wolframsyndrome.wustl.edu/